REMARKS

Claims 1-5 are pending in the application, and stand rejected by the PTO. For the reasons set forth below, Applicants respectfully traverse.

Specification

The Examiner has refused to enter the second substitute specification, submitted by Applicants on June 1, 2005. Specifically, the Examiner alleges that Applicants failed to submit a marked up copy showing changes to the specification relative to the immediate prior version according to the provisions of 37 C.F.R. § 1.125(c).

Applicants submit that the marked-up copy and clean copies of the substitute specification submitted on May 26, 2005, comply with 37 C.F.R. § 1.125(c). Applicants noted in the May 26, 2005 submission that the specification included no new matter, and that "[a]s indicated by the appropriate markings, all hyperlinks have been removed from the specification and all trademarks are represented in capital letters. The specification includes the paragraph in which Applicants assert their claim to priority." *Submission with Request for Continued Examination* at 3. Although Applicants previously submitted a marked-up copy of the specification, in the interest of advancing the prosecution of this application, Applicants re-submit herewith a duplicate copy of the marked up specification Applicants respectfully request that the substitute specification submitted on May 26, 2005 be entered.

Rejection Under 35 U.S.C. § 101/112 - Utility

The Examiner has maintained the rejection of Claims 1-5 as allegedly lacking a specific and substantial asserted utility or a well-established utility. The Examiner alleges that the specification lacks "critical information" such as whether the differences in nucleic acid expression of PRO300 are significant, under what conditions differences can be detected, what levels (relative or absolute) are detected in the tumor and normal tissue samples, sample size and probability of detection for any particular lung tumor type. Office Action at 6-7, 14. The Examiner recognizes that the nucleic acid of SEQ ID NO:11 is more highly expressed in normal lung tissue compared to lung tumor tissue, however, the Examiner declares that this "does not convey to the claimed antibodies," because as a whole, the prior art does not provide a reasonable

expectation that the expression of the nucleic acid of SEQ ID NO:11 positively correlates with the expression of the protein of SEQ ID NO:12. Office Action at 6. The Examiner cites Haynes *et al.*, Gygi *et al.*, Chen *et al.*, Fessler *et al.*, and Hu *et al.* for support for the position that one cannot assume that polypeptide and mRNA levels correlate with each other and that one cannot assume the changes in expression levels correlate with biological activity. The Examiner also continues to maintain the position that "gene copy number would be relevant to the data provided in the instant specification," and that Applicants' data are "suspect because there has been no correction for aneuploidy." Office Action at 7-8. In view of the above, the Examiner concludes that further research is necessary to determine whether PRO300 polypeptide levels are significantly decreased in lung tumor compared to lung tissue, and thus whether the claimed antibodies are useful as diagnostic tools.

Utility – Legal Standard

According to the Utility Examination Guidelines ("Utility Guidelines"), 66 Fed. Reg. 1092 (2001) an invention complies with the utility requirement of 35 U.S.C. § 101, if it has at least one asserted "specific, substantial, and credible utility" or a "well-established utility."

Under the Utility Guidelines, a utility is "specific" when it is particular to the subject matter claimed. For example, it is generally not enough to state that a nucleic acid is useful as a diagnostic tool without also identifying the condition that is to be diagnosed.

The requirement of "substantial utility" defines a "real world" use, and derives from the Supreme Court's holding in *Brenner v. Manson*, 383 U.S. 519, 534 (1966) stating that "The basic *quid pro quo* contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility." In explaining the "substantial utility" standard, M.P.E.P. § 2107.01 cautions, however, that Office personnel must be careful not to interpret the phrase "immediate benefit to the public" or similar formulations used in certain court decisions to mean that products or services based on the claimed invention must be "currently available" to the public in order to satisfy the utility requirement. "Rather, *any reasonable use that an applicant has identified for the invention that can be viewed as providing a public benefit should be accepted as sufficient,* at least with regard to defining a 'substantial' utility." (M.P.E.P. § 2107.01, emphasis added).

The mere consideration that further experimentation might be performed to more fully develop the claimed subject matter does not support a finding of lack of utility. M.P.E.P. § 2107.01 III cites *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995) in stating that "Usefulness in patent law ... necessarily includes the expectation of further research and development. The stage at which an invention in this field becomes useful is well before it is ready to be administered to humans." Further, "[T]o violate § 101 the claimed device must be totally incapable of achieving a useful result" *Juicy Whip Inc. v. Orange Bang Inc.*, 51 USPQ2d 1700 (Fed. Cir. 1999), *citing Brooktree Corp. v. Advanced Micro Devices, Inc.*, 977 F.2d 1555, 1571 (Fed.Cir.1992).

Indeed, the Guidelines for Examination of Applications for Compliance With the Utility Requirement, set forth in M.P.E.P. § 2107 II(B)(1) gives the following instruction to patent examiners: "If the applicant has asserted that the claimed invention is useful for any particular practical purpose ... and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility."

Finally, in assessing the credibility of the asserted utility, the M.P.E.P. states that "to overcome the presumption of truth that an assertion of utility by the applicant enjoys" the PTO must establish that it is "more likely than not that one of ordinary skill in the art would doubt (i.e., "question") the truth of the statement of utility." M.P.E.P. § 2107.02 III A. The M.P.E.P. cautions that:

> Rejections under 35 U.S.C. 101 have been **rarely sustained** by federal courts. Generally speaking, **in these rare cases**, the 35 U.S.C. 101 rejection was sustained either because the **applicant ... asserted a utility that could only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**. M.P.E.P. § 2107.02 III B. (underline emphasis in original, bold emphasis added); citing *In re Gazave*, 379 F.2d 973, 978, 154 USPQ 92, 96 (CCPA 1967).

Utility need NOT be Proved to a Statistical Certainty – a Reasonable Correlation between the Evidence and the Asserted Utility is Sufficient

An Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In re Langer*, 503 F.2d

1380, 1391, 183 USPQ 288, 297 (CCPA 1974). *See, also In re Jolles*, 628 F.2d 1322, 206 USPQ 885 (CCPA 1980); *In re Irons*, 340 F.2d 974, 144 USPQ 351 (1965); *In re Sichert*, 566 F.2d 1154, 1159, 196 USPQ 209, 212-13 (CCPA 1977). Compliance with 35 U.S.C. § 101 is a question of fact. *Raytheon v. Roper*, 724 F.2d 951, 956, 220 USPQ 592, 596 (Fed. Cir. 1983) cert. denied, 469 US 835 (1984). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The PTO has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

In *Fujikawa v. Wattanasin*, 93 F.3d 1559, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996), the Court of Appeals for the Federal Circuit upheld a PTO decision that *in vitro* testing of a novel pharmaceutical compound was sufficient to establish practical utility, stating the following rule:

> [T]esting is often required to establish practical utility. But the test results **need not absolutely prove** that the compound is pharmacologically active. All that is required is that the tests be "*reasonably* indicative of the desired [pharmacological] response." In other words, there must be **a sufficient correlation** between the tests and an asserted pharmacological activity so as to convince those skilled in the art, **to a reasonable probability**, that the novel compound will exhibit the asserted pharmacological behavior." *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1564, 39 U.S.P.Q.2d 1895 (Fed. Cir. 1996) (internal citations omitted, bold emphasis added, italics in original).

While the *Fujikawa* case was in the context of utility for pharmaceutical compounds, the principals stated by the Court are applicable in the instant case where the asserted utility is for a therapeutic and diagnostic use – utility does not have to be established to an absolute certainty, rather, the evidence must convince a person of skill in the art "to a reasonable probability." In addition, the evidence need not be direct, so long as there is a "sufficient correlation" between the tests performed and the asserted utility.

Thus, the legal standard for demonstrating utility is a relatively low hurdle. An Applicant need only provide evidence such that it is **more likely than not that a person of skill in the art would be convinced, to a reasonable probability, that the asserted utility is true**. The evidence need not be direct evidence, so long as there is a reasonable correlation between the evidence and the asserted utility. The Applicant **does not need to provide evidence such that it establishes an asserted utility as a matter of statistical certainty.**

Even assuming that the PTO has met its initial burden to offer evidence that one of ordinary skill in the art would reasonably doubt the truth of the asserted utility, Applicants assert that they have met their burden of providing rebuttal evidence such that it is more likely than not those skilled in the art, to a reasonable probability, would believe that the claimed invention is useful as a diagnostic tool for cancer.

Substantial Utility

Summary of Applicants' Arguments and the PTO's Response

In an attempt to clarify Applicants' argument, Applicants offer a summary of their argument and the disputed issues involved. Applicants assert that the claimed antibodies have utility as diagnostic tools for cancer, particularly lung cancer. Applicants are not asserting that the claimed antibodies will necessarily provide a definitive diagnosis of cancer, but rather that they are useful, alone or in combination with other diagnostic tools to assist in the diagnosis of lung cancer. Applicants' asserted utility rests on the following argument:

1. Applicants have provided reliable evidence that mRNA for the PRO300 polypeptide is more highly expressed in normal lung tissue compared to lung tumor; and

2. Applicants assert that it is well-established in the art that a **change** in the level of mRNA for a particular protein, e.g. a decrease, generally leads to a corresponding **change** in the level of the encoded protein, e.g. a decrease;

3. Given Applicants' evidence that the level of mRNA for the PRO300 polypeptide is decreased in lung tumor tissue compared to normal lung tissue, it is likely that the PRO300 polypeptide is also decreased in lung tumor tissue compared to normal lung tissue. Antibodies to polypeptides such as PRO300 which are differentially expressed in certain cancers are useful as diagnostic tools.

Applicants understand the Examiner to be making several arguments regarding the utility of the claimed antibodies:

1. The Examiner questions the reliability of Applicants' data and states that the specification does not provide "critical information" relating to the assay in Example 18;

2. The Examiner argues that the data have not been corrected for aneuploidy, rendering the results in the instant specification suspect; and

3. The Examiner argues that as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:11 positively correlates with the expression of the polypeptide of SEQ ID NO:12.

As detailed below, Applicants submit that the PTO has failed to meet its initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). The Examiner has failed to offer objective evidence to support her rejection of the data in Example 18 and the Declaration of Chris Grimaldi in support of these data. The Examiner has improperly required that Applicants disclose additional information regarding the assay presented in Example 18 to establish utility, and has improperly concluded that Applicants' data are suspect. Applicants have demonstrated that it is more likely than not that the skilled artisan would believe that PRO300 polypeptides are differentially expressed in normal lung compared to lung tumor, given Applicants' data demonstrating the differential expression of SEQ ID NO:11. Finally, even if the PTO has met its initial burden, Applicants have submitted enough rebuttal evidence to establish that it is **more likely than not** that a person of skill in the art would be convinced, **to a**

reasonable probability, that the asserted utility is true. As stated above, **the standard for establishing an asserted utility is not statistical or absolute certainty.**

Applicants have established that the gene encoding the PRO300 polypeptide is differentially expressed in lung cancers compared to normal lung tissue

Applicants first address the Examiner's argument that the evidence of differential expression of the gene encoding PRO300 in lung tumor is insufficient. The Examiner maintains that the specification does not set forth the statistical significance of the differential expression of PRO300, the assay conditions, number of samples tested, and the expression level range for normal and tumor tissues. The Examiner concludes that "the specification has not provided the invention in a form that can be used without necessary further experimentation." Office Action at 12. Thus, the Examiner appears to take the position that additional explanation of the experimental methods and results, beyond the disclosure provided in the specification at Example 18, is required in order for Applicants to initially establish a utility for the claimed antibodies.

Applicants submit that the Examiner's position that additional evidence must have been disclosed in order to initially establish the utility of the claimed antibodies is beyond that required under 35 U.S.C. §101. First, Applicants' statement of utility is presumed to be true, and further evidence to establish utility should not be required. See *In re Langer*, 503 F.2d at 1391, 183 USPQ at 297; *In re Malachowski*, 530 F.2d 1402, 1404, 189 USPQ 432, 435 (CCPA 1976); *In re Brana*, 51 F.3d 1560, 34 USPQ2d 1436 (Fed. Cir. 1995); M.P.E.P. §2107.02 (III). Requests for additional evidence should be imposed rarely, such as only when a statement is incredible in the light of the knowledge of the art, or factually misleading. *In re Citron*, 325 F.2d 248, 139 USPQ 516 (CCPA 1963); M.P.E.P. §2107.02 (V). Second, as the Examiner recognizes that "the nucleic acid of SEQ ID NO:11 is more highly expressed in normal lung compared to lung tumor tissue," (Office Action at 6), it is clear that the Examiner does not question that differential expression was observed. Nevertheless, the Examiner declares that without information regarding "whether differences in nucleic acid expression of PRO300 were significant. . .the skilled artisan cannot use. . .the claimed invention." Thus, the Examiner appears to be requiring that Applicants provide additional details to establish differential

expression of the nucleic acids and encoded polypeptides with statistical certainty to "convey utility" to the claimed antibodies. As stated above, **statistical certainty is not the proper standard for establishing utility**, and only a reasonable correlation between the observed activity and the asserted utility is required. See M.P.E.P. §2107.03(I).

Notwithstanding the presumption of utility that should be accorded to Applicants' claimed antibodies, Applicants previously submitted a copy of a first Declaration of J. Christopher Grimaldi, an expert in the field of cancer biology (attached as Exhibit 1 in the Response mailed January 3, 2005). As discussed previously, the declaration explains the importance of the data in Example 18, and how differential gene and protein expression studies are used to differentiate between normal and tumor tissue (see Declaration, paragraph 7).

In paragraphs 6 and 7, Mr. Grimaldi explains that the semi-quantitative analysis employed to generate the data of Example 18 is sufficient to determine if a gene is over- or under-expressed in tumor cells compared to corresponding normal tissue. He states that any visually detectable difference seen between two samples is indicative of at least a two-fold difference in cDNA between the tumor tissue and the counterpart normal tissue. Thus, the results of Example 18 reflect at least a two-fold difference between normal and tumor samples. He also states that the results of the gene expression studies indicate that the genes of interest "can be used to differentiate tumor from normal," thus establishing their reliability. He explains that, contrary to the Examiner's assertions, "*The precise levels of gene expression are irrelevant; what matters is that there is a relative difference in expression between normal tissue and tumor tissue.*" (Paragraph 7) (Emphasis added). Thus, since it is the relative level of expression between normal tissue and suspected cancerous tissue that is important, the precise level of expression in normal tissue is irrelevant. Likewise, there is no need for quantitative data to compare the level of expression in normal and tumor tissue. As Mr. Grimaldi states, "If a difference is detected, this indicates that the gene and its corresponding polypeptide and antibodies against the polypeptide are useful for diagnostic purposes, to screen samples to differentiate between normal and tumor." Applicants reiterate what is highlighted in Dr. Grimaldi's declaration -- namely that the expression level range for normal and tumor tissues is not important to confer utility on the claimed antibodies as diagnostic tools. The Examiner has

not provided a basis for the conclusion to cast doubt on Dr. Grimaldi's assertion that that the precise levels of differential gene expression are irrelevant.

In paragraph 5 of his declaration, Mr. Grimaldi states that the gene expression studies reported in Example 18 of the instant application were made from pooled samples of normal and of tumor tissues. Mr. Grimaldi explains that:

> The DNA libraries used in the gene expression studies were made from pooled samples of normal and of tumor tissues. *Data from pooled samples is more likely to be accurate than data obtained from a sample from a single individual.* That is, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. (Paragraph 5) (emphasis added).

The Examiner rejects Dr. Grimaldi's assertion that data from pooled samples are more likely to be accurate than data from a single individual, stating that data from pooled samples "begs the question of whether the tissue from an individual could be assessed for whether or not it is cancerous. ... Clinical diagnostics are not usually geared toward a populous but towards an individual's particular condition." Office Action at 14. The Examiner provides no basis for rejecting Dr. Grimaldi's assertion that data from pooled samples is not more accurate than if Applicants had presented data from an individual, as Dr. Grimaldi testified. As Dr. Grimaldi explained, the detection of variations in gene expression is likely to represent a more generally relevant condition when pooled samples from normal tissues are compared with pooled samples from tumors in the same tissue type. . Contrary to the Examiner's assertion, clinical diagnostics typically measure a generally relevant condition (*e.g.* differential expression of a particular gene) present in a populous (*e.g.* a population of individuals with lung cancer).

In further response to Applicants' evidence, the Examiner also argues that "there is no suggestion of multiple tumors tested." Office Action at 17. Applicants disagree. Dr. Grimaldi's assertion that the [c]DNA libraries used in the gene expression studies were made from pooled samples clearly indicates that "multiple tumors" were tested.

Applicants submit that the declaration of Mr. Grimaldi is based on personal knowledge of the relevant facts at issue. Mr. Grimaldi is an expert in the field and conducted or supervised the experiments at issue. Applicants remind the Examiner that "[o]ffice personnel must accept an opinion from a qualified expert that is based upon relevant facts whose accuracy is not being

questioned." PTO Utility Examination Guidelines (2001) (emphasis added). In addition, declarations relating to issues of fact should not be summarily dismissed as "opinions" without an adequate explanation of how the declaration fails to rebut the Examiner's position. *In re Alton* 76 F.3d 1168 (Fed. Cir. 1996).

The Examiner also asserts that "without more specifics about expression level range for normal and tumor tissues, specific types of lungl [*sic*] tumors detectable, and probability of detection for any particular lung tumor type, (*e.g.*, whether one would reasonably expect higher expression in 10/10 or 1/20 tumors tested)," the specification has not provided the invention in an enabling form. Office Action at 13. Thus, the Examiner appears to take the position that yet even further additional data and evidence must be disclosed in order for Applicants to initially establish a utility for the claimed antibodies. Applicants submit that the Examiner's prerequisite of additional evidence is simply beyond that necessary to establish utility. Applicants remind the Examiner that "[a]n invention does not lack utility merely because [it] lacks perfection or performs crudely," and that "even if an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate." *In re Brana*, 51 F.3d 1560 (Fed. Cir. 1995). The Examiner's elevated standard for utility is improper. Whether the claimed antibodies will detect 10/10 or 1/20 lung tumors relates to the degree of "perfection" of PRO300 as diagnostic tools, not to whether or not the claimed antibodies are useful as diagnostic tools *per se*. Likewise, the Examiner's assertion that "the lack of information regarding types of tumors weighs heavily on the enablement of the claimed invention" is inappropriate. To illustrate the alleged necessity of disclosing the type of lung tumors exhibiting differential expression of PRO300, the Examiner states that "[i]f the gene is not expressed in stage 3 adenocarcinomas, one of ordinary skill in the art would not be able to make a correct diagnosis of lung tumor for a stage 1 adeonocarcinoma of the lung because it would be a false negative result." Office Action at 16. Applicants reiterate that they are not asserting that the claimed antibodies will provide a definitive diagnosis of cancer, but rather that they are useful alone or in combination with other diagnostic tools to assist in the diagnosis of lung cancer. The Examiner's requirement that Applicants demonstrate *probability of detection*, and *specific types of lung tumors detectable*, simply goes beyond what is required to demonstrate that Applicants' claimed invention is credible.

Applicants submit that the asserted utility for the claimed antibodies based on the disclosure, in combination with the first Grimaldi declaration is not "incredible in the light of the knowledge in the art, or factually misleading." *In re Citron*, 325 F.2d at 253. Therefore, the Examiner's requests and requirements for additional information are improper. Even for inventions claiming a pharmacological or therapeutic utility, the Federal courts have consistently reversed rejections by the PTO asserting a lack of utility where an applicant has provided evidence supporting the utility. *See M.P.E.P.* §2107.03. Applicants have provided evidence in both Example 18 and the Declarations and other exhibits that describe the assay methods and interpretation of results, and demonstrate the correlation between changes in mRNA and changes in protein levels as detailed above. Thus, Applicants have provided a variety of evidence supporting the utility of the claimed antibodies. Accordingly, the requirement for Applicants to provide additional evidence is unwarranted.

Reports of pre-cancerous instances of aneuploidy do not cast doubt on Applicants' differential expression data

The Examiner has maintained her position that gene copy number is relevant to the data provided in the instant specification. The Examiner asserts that "[i]f the nucleic acid molecule being amplified by Applicant [*sic*] is from a gene with an increased copy number due to aneuploidy, then the results in the instant specification are suspect because there has been no correction for aneuploidy." Office Action at 8. The Examiner states that Hittelman *et al.* establish that damaged pre-cancerous lung epithelium is often aneuploid, and goes on to conclude that "[b]ecause aneuploid DNA can be found in normal tissue, detection of increased DNA copy number does not necessary [*sic*] mean that those cells containing the DNA are cancerous." *Id.* Applicants respectfully disagree.

As an initial matter, Applicants reiterate that the data in Example 18 do not relate to detection of increased DNA copy number, but rather differences in mRNA levels as detected by quantitative amplification and detection of cDNA. Additionally, the Examiner's assertion that "detection of increased DNA copy number does not necessarily mean that those cells are cancerous" does not cast doubt on Applicants' data demonstrating decreased levels of PRO300 mRNA in lung tumor compared to normal lung tissue. Further, Applicants submit that the

premise of Hittelman is that detection of aneuploidy can be a reliable indicator of a pre-cancerous/pre-malignant state. For example, Hittelman states that "studies of the premaligant lesions. . .have provided evidence for a gradual accumulation of genetic alterations accompanied by evidence for dysregulation of cellular control mechanisms." Hittelman at 5. Hittelman concludes that detection of polysomy (three or more copies of a chromosome) is useful for monitoring the process of tumorigenesis, with increasingly higher percentages of cells exhibiting polysomy in normal, hyperplastic tissue, and tumor tissue, respectively. Hittelman is completely silent as to the mRNA levels in premalignant versus malignant lesions. Accordingly, Applicants submit that Hittelman does not render "the results in the instant specification. . .suspect." Office Action at 8.

Applicants have established that the accepted understanding in the art is that there is a direct correlation between changes in mRNA levels and changes in encoded protein levels

Applicants next demonstrate that it is well-established in the art that a **change** in the level of mRNA for a particular protein, generally leads to a corresponding **change** in the level of the encoded protein. As stated above, given Applicants' evidence of differential expression of the mRNA for the PRO300 polypeptide in lung tumor, it is likely that the PRO300 polypeptide is differentially expressed, and proteins differentially expressed in certain tumors, and antibodies to those proteins, have utility as diagnostic tools.

As shown by the declarations, references, and textbooks discussed below, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene.

Applicants previously submitted a copy of a second Declaration by J. Christopher Grimaldi, an expert in the field of cancer biology. As stated in paragraph 5 of the declaration, "Those who work in this field are well aware that in the vast majority of cases, when a gene is over-expressed...the gene product or polypeptide will also be over-expressed.... This same principal applies to gene under-expression." Further, "the detection of increased mRNA expression is expected to result in increased polypeptide expression, and the detection of

decreased mRNA expression is expected to result in decreased polypeptide expression. The detection of increased or decreased polypeptide expression can be used for cancer diagnosis and treatment." The references cited in the declaration and submitted herewith support this statement.

Applicants also previously submitted a copy of the declaration of Paul Polakis, Ph.D., an expert in the field of cancer biology. As stated in paragraph 6 of his declaration:

> Based on my own experience accumulated in more than 20 years of research, including the data discussed in paragraphs 4 and 5 above [showing a positive correlation between mRNA levels and encoded protein levels in the vast majority of cases] and my knowledge of the relevant scientific literature, it is my considered scientific opinion that for human genes, an increased level of mRNA in a tumor cell relative to a normal cell typically correlates to a similar increase in abundance of the encoded protein in the tumor cell relative to the normal cell. In fact, *it remains a central dogma in molecular biology that increased mRNA levels are predictive of corresponding increased levels of the encoded protein.* (Emphasis added).

Dr. Polakis acknowledges that there are published cases where such a correlation does not exist, but states that it is his opinion, based on over 20 years of scientific research, that "such reports are exceptions to the commonly understood general rule that increased mRNA levels are predictive of corresponding increased levels of the encoded protein." (Polakis Declaration, paragraph 6).

The statements of Grimaldi and Polakis are supported by the previously-submitted teachings in Molecular Biology of the Cell, a leading textbook in the field (Bruce Alberts, *et al.*, Molecular Biology of the Cell (3rd ed. 1994) and (4th ed. 2002)). Figure 9-2 of Alberts 3rd ed. shows the steps at which eukaryotic gene expression can be controlled. The first step depicted is transcriptional control. Alberts 3rd ed. provides that "[f]or most genes transcriptional controls are paramount. This makes sense because, of all the possible control points illustrated in Figure 9-2, only transcriptional control ensures that no superfluous intermediates are synthesized." Alberts 3rd ed. at 403 (emphasis added). In addition, the text states that "Although controls on the initiation of gene transcription are the predominant form of regulation for most genes, other controls can act later in the pathway from RNA to protein to modulate the amount of gene product that is made." Alberts 3rd ed. at 453 (emphasis added). Thus, as established in Alberts

3rd ed., the predominant mechanism for regulating the amount of protein produced is by regulating transcription initiation.

In Alberts 4th ed., Figure 6-3 on page 302 illustrates the basic principle that there is a correlation between increased gene expression and increased protein expression. The accompanying text states that "a cell can change (or regulate) the expression of each of its genes according to the needs of the moment – *most obviously by controlling the production of its mRNA*." Alberts 4th ed. at 302 (emphasis added). Similarly, Figure 6-90 on page 364 of Alberts 4th ed. illustrates the path from gene to protein. The accompanying text states that while potentially each step can be regulated by the cell, "the initiation of transcription is the most common point for a cell to regulate the expression of each of its genes." Alberts 4th ed. at 364 (emphasis added). This point is repeated on page 379, where the authors state that of all the possible points for regulating protein expression, "[f]or most genes transcriptional controls are paramount." Alberts 4th ed. at 379 (emphasis added).

Further support for Applicants' position can be found in the previously-submitted textbook excerpt from Genes VI, (Benjamin Lewin, Genes VI (1997)) which states "having acknowledged that control of gene expression can occur at multiple stages, and that production of RNA cannot inevitably be equated with production of protein, it is clear that the overwhelming majority of regulatory events occur at the initiation of transcription." *Genes VI* at 847-848 (emphasis added).

Additional support is also found in the previously submitted publication by Zhigang *et al.*, World Journal of Surgical Oncology 2:13, 2004. Zhigang studied the expression of prostate stem cell antigen (PSCA) protein and mRNA to validate it as a potential molecular target for diagnosis and treatment of human prostate cancer. The data showed "a high degree of correlation between PSCA protein and mRNA expression." Zhigang at 4. Of the samples tested, 81 out of 87 showed a high degree of correlation between mRNA expression and protein expression. The authors conclude that "it is demonstrated that PSCA protein and mRNA overexpressed in human prostate cancer, and that the increased protein level of PSCA was resulted from the upregulated transcription of its mRNA." Zhigang at 6. Even though the correlation between mRNA expression and protein expression occurred in 93% of the samples tested, not 100%, the authors

state that "PSCA may be a promising molecular marker for the clinical prognosis of human Pca and a valuable target for diagnosis and therapy of this tumor." Zhigang at 7.

Further, the previously submitted publication by Meric *et al.*, Molecular Cancer Therapeutics, vol. 1, 971-979 (2002), states the following:

> The **fundamental principle** of molecular therapeutics in cancer is to exploit the differences in gene expression between cancer cells and normal cells...[M]ost efforts have concentrated on identifying differences in gene expression at the level of mRNA, which can be attributable to either DNA amplification or to differences in transcription. Meric *et al.* at 971 (emphasis added).

Those of skill in the art would not be focusing on differences in gene expression between cancer cells and normal cells if there were no correlation between gene expression and protein expression.

In response to Applicants' evidence, the Examiner states that "while one can find prior art that supports a 'significant probability' that mRNA and protein levels will correlate, there is influential prior art of record that requires the Examiner to maintain that, as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:11 positively correlates with the expression of the protein of SEQ ID NO:12... The advent of proteome analysis has only recently begun to elucidate the reality of nucleic acid and protein expression which is becoming recognized as more complicated and different from the previously accepted dogma." Office Action at 9. (Emphasis added). "It is essential for Office personnel to recognize, fully consider and respond to each substantive element of any response to a rejection based on lack of utility." M.P.E.P. 2107.02 VI. Regarding Zhigang *et al,* the Examiner merely states that "[t]here is no requirement for utility that 100% correlation be present . . Nevertheless, in the instance [*sic*] application we have no correlation." Applicants submit that this does not respond to Applicants' assertion that Zhigang *et al.* illustrates that the skilled artisan would more likely than not believe that, generally, changes in mRNA levels correlate with changes in protein levels. The Examiner's discussion of Meric is similar:

> Applicants argue the [*sic*] Meric et al. says that cancer therapeutics relies on exploiting differences in gene expression between cancer and normal cells. While this is generally true, the instantly claimed invention cannot be used as a cancer therapeutic or diagnostic because of the information missing to support such a use. Office Action at 18 (Emphasis added)

In summary, in response to Applicants' evidence the Examiner states that the art supports a "significant probability" that mRNA and protein levels will correlate, that "there is no requirement for utility that 100% correlation be present," and that it is "generally true" that those skilled in the art rely upon differences in gene expression in designing cancer diagnostics and therapeutics. Nevertheless, the Examiner concludes that "as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:11 positively correlates with the expression of the protein of SEQ ID NO:12," or that it is more likely than not that the skilled artisan would believe Applicants' asserted utility.

The Examiner states that the art "demonstrate[s] that the dogma relied upon by Applicants and the Declarants is not a law of nature." Office Action at 13. The prior art relied upon by the Examiner as allegedly demonstrating that there is no "reasonable expectation" that mRNA and protein levels correlate is Haynes *et al.*, Gygi *et al.*, Chen *et al.*, Fessler *et al.*, and Hu *et al.*, each of which is discussed below. For the reasons discussed previously, and reiterated below, Haynes, Gygi, Chen, Fessler and Hu are not contrary to Applicants' asserted utility.

Haynes studied whether there is a correlation between the level of mRNA expression and the level of protein expression for 80 selected genes from yeast. The genes were selected because they constituted a relatively homogeneous group with respect to predicted half-life and expression level of the protein products. *See* Haynes at 1863. Haynes did not examine whether a **change** in transcript level for a particular gene led to a **change** in the level of expression of the corresponding protein. Instead, Haynes determined whether the steady-state transcript level correlated with the steady-state level of the corresponding protein based on an analysis of 80 different genes.

Haynes reported to have "found a general trend but no strong correlation between protein and transcript levels." *Id.* However, a cursory inspection of Fig. 1 shows a clear correlation between the mRNA levels and protein levels measured. This correlation is confirmed by an inspection of the full-length research paper from which the data in Fig. 1 were derived, (Gygi *et al.*, Molecular and Cellular Biology, Mar. 1999, 1720-1730, previously submitted as Exhibit 2). Gygi states that "there was a general trend of increased protein levels resulting from increased mRNA levels," with a correlation coefficient of 0.935, indicating a strong correlation. Gygi at 1726. Moreover, Gygi also states that the correlation is especially strong for highly expressed

mRNAs. *Id.* Thus, it is not clear that Haynes even supports the Examiner's position, as Haynes did report a general trend, and, contrary to the Examiner's position that the teachings of Gygi demonstrate that "no meaningful infomraiton regarding protein expression can be gleaned fromt eh data presented in Example 18 (Office Action at 20), Gygi reports a strong correlation between increasing mRNA levels and increasing protein levels.

The Examiner focuses on the portion of Haynes where the authors reported that for some of the studied genes with equivalent mRNA levels, there were differences in corresponding protein expression, including some that varied by more than 50-fold. Similarly, Haynes reports that different proteins with similar expression levels were maintained by transcript levels that varied by as much as 40-fold. *Id.* Thus, Haynes showed that for one type of yeast, similar mRNA levels for *different* genes did not universally result in equivalent protein levels for the *different* gene products, and similar protein levels for *different* gene products did not universally result from equivalent mRNA levels for the *different* genes. These results are expected, since there are many factors that determine translation efficiency for a given transcript, or the half-life of the encoded protein. Not surprisingly, based on these results, Haynes concluded that protein levels cannot always be accurately predicted from the level of the corresponding mRNA transcript *when looking at the level of transcripts across different genes.*

Importantly, Haynes did not say that for a single gene, the level of mRNA transcript is not positively correlated with the level of protein expression. Applicants have asserted that increasing or decreasing the level of mRNA for the same gene leads to an increase or decrease for the corresponding protein. Haynes did not study this issue and says absolutely nothing about it. Therefore, Haynes is not inconsistent with or contradictory to the utility of the instant claims, and offers no support for the Examiner's position.

Applicants' respectfully submit that the fact that both Haynes and Gygi looked at static levels of mRNA across different genes, not changes in the level of expression for a single gene, render these references inapplicable to Applicants' asserted utility. As discussed above, when Haynes and Gygi state that protein levels cannot be accurately predicted from the level of the corresponding mRNA, they are referring only to the static level of mRNA. Applicants have not asserted that protein levels can be predicted from static levels of mRNA, and the asserted utility does not depend on there being a correlation between static levels of mRNA and protein across

different genes. Instead, Applicants have asserted that **changes** in mRNA level for an individual gene are generally correlated with **changes** in the level of the encoded protein. Applicants have asserted that because there is a change in the level of mRNA for PRO300 in lung tumors compared to normal lung tissue, the level of PRO300 protein will show a similar change. Predicting the absolute level of protein from the static level of mRNA is not required for this asserted utility since it is the change in the level of mRNA and protein that is important. Haynes and Gygi have absolutely no bearing on this issue since they examined static levels of mRNA for different genes.

The Examiner also cites Chen *et al.* for support for the assertion that polypeptide levels cannot be accurately predicted from mRNA levels. In Chen, the authors examined the relationship between mRNA levels and protein levels in 76 lung adenocarcinomas and 9 non-tumor lung samples. Like Haynes, Chen examined the global relationship between mRNA and the corresponding protein abundance by calculating the average mRNA and protein level of all the samples for each gene or protein, and then looked for a correlation across different genes. As discussed above with respect to Haynes, this measurement of a correlation across genes is not relevant to Applicants' asserted utility. Chen also looked at the level of mRNA of 98 individual genes and their corresponding proteins across the samples. Chen reports that 21.4% (21 of 98) of the genes showed a statistically significant correlation between protein and mRNA expression.

Chen provides scant evidence to counter Applicants' asserted utility for the claimed antibodies because portions of Chen support Applicants' assertions, and the remaining portions provide little insight into the relationship between mRNA levels and corresponding protein levels for mRNA that is differentially expressed in tumor cells relative to normal cells. Rather than looking for mRNAs which were differentially expressed, Chen merely selected proteins whose identity could be determined regardless of any changes in expression level (Chen at 306, right column). Importantly, it is not known if there was any substantial difference in mRNA levels for the various genes across samples – in short, with the exception of the genes in Figures 2A-2C, it is not known if the genes examined were differentially expressed. Also of significance for Applicants' asserted utility is the fact that Chen did not attempt to examine any differential expression between the cancerous lung samples and the non-cancerous lung samples – Chen did not distinguish between cancer and normal samples in their analysis.

Applicants have asserted that changes in mRNA levels, particularly those which are two-fold or greater, will correspond with measurable changes in polypeptide expression. The data in Chen support Applicants' assertion. In Figures 2A-2C, Chen plots mRNA value vs. protein value for three genes. In these figures, a wide range of mRNA expression levels were observed (approximately seven- to eight-fold), and a correlation between mRNA and protein levels was observed for all three mRNA/protein pairs. This supports Applicants' asserted correlation between changes in mRNA levels which are two-fold or greater and changes in polypeptide expression.

The Examiner relies on the fact that Chen also reports a lack of correlation for some mRNA/protein pairs to support its assertion that polypeptide levels cannot be accurately predicted from mRNA levels. However, the lack of correlation reported by Chen could be a result of a lack of substantial changes in mRNA level. This can be understood by again turning to Figures 2A-2C. As noted above, where a wide range of mRNA expression levels is seen, a correlation between mRNA and protein levels is observed. However, if one examines the data points within a small range of mRNA levels for these same genes, e.g. 500-600 or 5000-6000 in Figs. 2A-2C, it is clear that a correlation would not be detected for the data within this range. This does not mean that a correlation between changes in mRNA and protein does not exist for these genes, as is evident when larger changes in mRNA expression are included in the analysis. Instead, this indicates that for relatively small changes in mRNA, any correlation is masked by imprecision in the measurements.

Chen's experiment compared mRNA levels vs. protein levels across samples without selecting mRNA that showed a difference in expression level. And unlike Applicants, Chen did not examine differences in mRNA between tumor and normal tissue. Since almost all samples tested by Chen were from the same type of tissue, few substantial variations in the level of mRNA or protein for a particular gene across the samples tested would be expected. Instead, it would be expected that most genes examined by Chen would have similar mRNA or protein levels across the samples. Figures 2A-2C of Chen demonstrate that the methods utilized by Chen cannot detect correlations between mRNA and protein levels when only small differences in mRNA expression are observed, but a correlation is detected when larger differences in mRNA expression are observed.

Accordingly, the only data reported by Chen which shows substantial changes in the expression of mRNA, Figures 2A-C, confirms Applicants' assertion that substantial changes in mRNA levels (e.g., 2-fold or greater) will correspond to substantial changes in polypeptide expression. Further, this data also explains the lack of observed correlation between mRNA levels and protein levels for other genes reported by Chen. Thus, even given Chen's inability to detect a correlation between mRNA and protein in some genes, Chen's results do not refute Applicants' position.

Instead, Chen supports Applicants' position that a significant correlation between mRNA and protein levels exists for changes in mRNA levels that are 2-fold or greater. In further support of Applicants' position, Chen cites Celis *et al.* (FEBS Lett., 480:2-16 (2000)) stating that the authors "found a good correlation between transcript and protein levels among 40 well resolved, abundant proteins using a proteomic and microarray study of bladder cancer." *Chen* at 311, first column (emphasis added). As mentioned above, the lack of a correlation across genes is not relevant to Applicants' asserted utility, and therefore Chen's discussion of this issue and citation of Anderson and Seilhamer (Electrophoresis, 18:533-37 (1997)) and Gygi *et al.* (Mol. Cell. Bio., 19:1720-30 (1999)) offer no support for the Examiner's position.

Even if the results in Chen supported the Examiner's argument, which they do not as discussed above, one contrary example does not establish that one of skill in the art would find it is more likely than not there is no general correlation between changes in mRNA level and changes in protein level for an individual gene. There are other non-transcriptional mechanisms for regulating gene and protein expression (*i.e.*, post-transcriptional regulation of genes, translation efficiency, etc.). However, as shown by the declarations, references, and textbooks discussed above, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between **changes** in mRNA levels and **changes** in protein levels for a particular gene.

The Examiner also cites a publication by Fessler *et al.* For the reasons discussed below, Fessler is not contrary to Applicants' asserted utility. Applicants submit that, if anything, Fessler supports Applicants' assertions in support of utility of the claim polypeptides.

Applicants submit that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. Applicants make no assertions regarding changes in protein levels when mRNA levels are unchanged, nor does evidence of changes in protein levels when mRNA levels are unchanged have any relevance to Applicants' assertion.

Fessler *et al.* studied changes in neutrophil (PMN) gene transcription and protein expression following lipoplysaccharide (LPS) exposure. Fessler lists in Table VIII a comparison of the change in the level of mRNA for 13 up-regulated proteins and 5 down-regulated proteins. Of the 13 up-regulated proteins, a change in mRNA levels is reported for only 3 such proteins. For these 3, mRNA levels are increased in 2 and decreased in the third. Of the 5 down-regulated proteins, a change in mRNA is reported for 3 such proteins. In all 3, mRNA levels also are decreased. Thus, in 5 of the 6 cases for which a change in mRNA levels are reported, the change in the level of mRNA corresponds to the change in the level of the protein. This is consistent with Applicants assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Regarding the remainder of the proteins listed in Table VIII, in 6 instances, protein levels changed while mRNA levels were unchanged. This evidence has no relevance to Applicants' assertion that changes in mRNA levels lead to corresponding changes in protein levels, since Applicants are not asserting that changes in mRNA levels are the only cause of changes in protein levels. In accounting for these results, Fessler explains that LPS has post-transcriptional activity that can influence protein levels (Fessler at 31300, right column). Nothing in these results by Fessler suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein. Accordingly, these results are not contrary to Applicants' assertions.

In the final 6 instances listed in Table VIII, protein levels changed while mRNA was noted as "absent." This evidence also has no relevance to Applicants' assertion that changes in mRNA levels causes corresponding changes in protein levels. By virtue of being "absent," it is not possible to tell whether mRNA levels were increased or decreased in PMN upon contact with LPS. Regarding these instances, Fessler explained that LPS may have post-translational activity that can result in increased protein stability (Fessler at 31300, right column). Nothing in these

results by Fessler suggests that a change in the level of mRNA for a particular protein does not generally lead to a corresponding change in the level of the encoded protein. Accordingly, these results also are not contrary to Applicants' assertions.

The Examiner points to Fessler's statement regarding Table VIII that "a poor correlation was found between corresponding transcripts and proteins." (Fessler at 31300, right column). As is clear from the above discussion, this statement does not relate to a lack of correlation between a change in mRNA levels leading to a change in protein levels, because in 5 of 6 such instances, changes in mRNA and protein levels correlated well. Instead, this statement relates to observations in which protein levels changed when mRNA was either unchanged or "absent." As such, this statement is an observation that in addition to transcriptional activity, LPS also has post-transcriptional and possibly post-translational activity that affect protein levels, an observation which is irrelevant to Applicants' assertions.

Thus, Fessler's results suggest that LPS has a transcriptional activity that can cause changes in mRNA levels which correlate with changes in protein levels, and that LPS also has post-transcriptional activity that can cause changes in protein levels that are not related to changes in mRNA levels. Accordingly, Fessler's results are consistent with Applicants' assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein.

Even if Fessler's results had shown that a change in the level of mRNA did not generally lead to a corresponding change in the level of the encoded protein, which they did not, the accuracy of Fessler's results is uncertain. Fessler admits that there were "limitations" to the results reported. These limitations included: possible artifactual transcript-protein discordance due to a 4 hour delay in harvesting after LPS exposure; uncertain post-incubation but pre-electrophoresis effects on protein synthesis, degranulation and exocytosis; and limited ability to quantitate protein amounts using Coomassie Blue. (Fessler at 31301, left column). Fessler exemplifies one such spurious result, in which there was a disparity between observed increase in cytokine mRNA, but an absence of detected cytokine proteins, which, as Fessler explains, "reflects their removal in the post-LPS incubation wash." (Fessler at 31297, right column). Thus, Fessler acknowledges "limitations" to the conclusion that, for some genes, transcript levels did not coincide well with corresponding protein levels, leaving it uncertain the extent to which

actual changes in protein levels differed from mRNA levels when neutrophils were exposed to LPS.

As such, Fessler does not represent "influential art ... that requires the Examiner maintain that as a whole, the prior art does not provide a reasonable expectation that expression of the nucleic acid of SEQ ID NO:11 positively correlates with the expression of the protein of SEQ ID NO:12." Office Action at 9. Instead, Fessler represents a teaching that LPS might cause transcriptional changes that correlate with changes in protein levels, and might also cause post-transcriptional changes in protein levels when mRNA levels are unchanged. Accordingly, Fessler is not contrary to Applicants' asserted utility.

Finally, the Examiner, although noting that "there are shortcomings of the technique used by Hu et al, [(J. Proteome Res., 2(4):405-12 (2003)], urges that the findings of Hu are suggestive of a correlation between expression level and activity. The Examiner notes that Hu demonstrates that "[e]ven when expression changes are statistically significant, it is not always clear if they are biologically meaningful." Office Action at 19. Applicants reiterate that the findings of Hu *et al.* do not support the Examiner's position that the skilled artisan would not have a reasonable expectation that differential expression of mRNA encoding PRO300 polypeptides will correlate with differential expression of PRO300 polypeptides. In other words, Hu is not relevant to statements in the declaration of Mr. Grimaldi that support the diagnostic utility of the claimed antibodies.

In Hu, the researchers used an automated literature-mining tool to summarize and estimate the relative strengths of all human gene-disease relationships published on Medline. They then generated a microarray expression dataset comparing breast cancer and normal breast tissue. Using their data-mining tool, they looked for a correlation between the strength of the literature association between the gene and breast cancer, and the magnitude of the difference in expression level. They report that for genes displaying a 5-fold change or less in tumors compared to normal, there was no evidence of a correlation between altered gene expression and a *known* role in the disease. *See* Hu at 411. However, among genes with a 10-fold or more change in expression level, there was a strong correlation between expression level and a *published* role in the disease. *Id.* at 412. Importantly, Hu reports that the observed correlation was only found among estrogen receptor-positive tumors, not ER-negative tumors. *Id.*

The general findings of Hu are not surprising – one would expect that genes with the greatest change in expression in a disease would be the first targets of research, and therefore have the strongest known relationship to the disease as measured by the number of publications reporting a connection with the disease. The correlation reported in Hu only indicates that the greater the change in expression level, the more likely it is that there is a *published* or *known* role for the gene in the disease, as found by their automated literature-mining software. Thus, Hu's results merely reflect a bias in the literature toward studying the most prominent targets, and reflect nothing regarding the ability of a gene that is 2-fold or more differentially expressed in tumors to serve as a disease marker.

Hu acknowledges the shortcomings of this method in explaining the disparity in Hu's findings for ER-negative versus ER-positive tumors: Hu attributes the "bias in the literature" toward the more prevalent ER-positive tumors as the explanation for the lack of any correlation between number of publications and gene expression levels in less-prevalent (and, therefore, less studied) ER-negative tumors. *Id.* Because of this intrinsic bias, Hu's methodology is unlikely to ever note a correlation of a disease with less differentially-expressed genes and their corresponding proteins, regardless of whether or not an actual relationship between the disease and less differentially-expressed genes exists. Accordingly, Hu's methodology yields results that provide little or no information regarding biological significance of genes with less than 5-fold expression change in disease. Nowhere in Hu does it say that a lack of correlation in their study means that genes with a less than five-fold change in level of expression in cancer cannot serve as molecular markers of cancer.

Applicants submit that a lack of known role for PRO300 in cancer does not prevent its use as a diagnostic tool for cancer. There is a difference between use of a gene for distinguishing between tumor and normal tissue on the one hand, and establishing a role for the gene in cancer on the other. Genes with lower levels of change in expression may or may not be the most important genes in causing the disease, but the genes can still show a consistent and measurable change in expression. While such genes may or may not be good targets for further research, they can nonetheless be used as diagnostic tools. Thus, Hu does not refute the Applicants' assertion that the PRO300 gene, polypeptide and associated antibodies can be used as cancer diagnostic tools because of the differential expression in certain tumors.

Applicants submit that a lack of known role of the encoded gene product of PRO300 in cancer does not prevent its use as a diagnostic tool for cancer. The PTO has recognized that the utility of a nucleic acid does not depend on the function of the encoded gene product. The Utility Examination Guidelines published on January 5, 2001 state "In addition, the utility of a claimed DNA does not necessarily depend on the function of the encoded gene product. A claimed DNA may have a specific and substantial utility because, e.g. it hybridizes near a disease-associated gene or it has a gene regulating activity." (Federal Register, Volume 66, page 1095, Comment 14). While Applicants appreciate that actions taken in other applications are not binding on the PTO with respect to the present application, Applicants note that the PTO issues patents relating to nucleic acids which are useful for diagnosing particular conditions regardless of whether the nucleic acids are the causative agent for the condition. For example, polymorphisms which are indicative of a predisposition to a particular condition are patentable (*see, e.g.,* U.S. Patent No. 6,465,185, U.S. Patent No. 6,228,582, and U.S. Patent No.6,162,604 submitted as Exhibits 2-4 in the Response mailed April 15, 2005), even though they may or may not cause the disease itself. Similarly, the present nucleic acids, polypeptides and antibodies, which are useful for determining whether an individual has cancer, are useful regardless of whether or not they are the cause of the cancer.

Further, the position of the Examiner is inconsistent with the analogous standard for therapeutic utility of a compound that "the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an 'immediate benefit to the public' and thus satisfies the utility requirement." M.P.E.P. §2701.01 (emphasis in original). Here, the mere identification of altered expression in tumors is relevant to the diagnosis of tumors, and, therefore, provides an immediate benefit to the public.

The Arguments made by the Examiner are not sufficient to satisfy the Examiner's initial burden of offering evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility"

As stated above, an Applicant's assertion of utility creates a presumption of utility that will be sufficient to satisfy the utility requirement of 35 U.S.C. § 101, "unless there is a reason for one skilled in the art to question the objective truth of the statement of utility or its scope." *In*

re Langer, 503 F.2d 1380, 1391, 183 USPQ 288, 297 (CCPA 1974). The evidentiary standard to be used throughout *ex parte* examination in setting forth a rejection is a preponderance of the evidence, or "more likely than not" standard. *In re Oetiker*, 977 F.2d 1443, 1445, 24 USPQ2d 1443, 1444 (Fed. Cir. 1992). This is stated explicitly in the M.P.E.P.:

> [T]he applicant does not have to provide evidence sufficient to establish that an asserted utility is true "beyond a reasonable doubt." **Nor must the applicant provide evidence such that it establishes an asserted utility as a matter of statistical certainty**. Instead, evidence will be sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true. M.P.E.P. at § 2107.02, part VII (2004) (underline emphasis in original, bold emphasis added, internal citations omitted).

The Examiner has the initial burden to offer evidence "that one of ordinary skill in the art would reasonably doubt the asserted utility." *In re Brana*, 51 F.3d 1560, 1566, 34 U.S.P.Q.2d 1436 (Fed. Cir. 1995). Only then does the burden shift to the Applicant to provide rebuttal evidence. *Id.* As stated in the M.P.E.P., such rebuttal evidence does not need to absolutely prove that the asserted utility is real. Rather, the evidence only needs to be reasonably indicative of the asserted utility.

Applicants remind the Examiner that the M.P.E.P. cautions that rejections for lack of utility are rarely sustained by federal courts, and that generally speaking, a utility rejection was sustained because the applicant asserted a utility "that could **only be true if it violated a scientific principle, such as the second law of thermodynamics, or a law of nature, or was wholly inconsistent with contemporary knowledge in the art**." M.P.E.P. § 2107.02 III B., citing *In re Gazave*, 379 F.2d 973, 978, 154 U.S.P.Q. 92, 96 (CCPA 1967) (underline emphasis in original, bold emphasis added). Rather than being wholly inconsistent with contemporary knowledge in the art, Applicants' asserted utility is squarely within the teaching of leading textbooks in the field, and is supported by references and the declarations of skilled experts.

The Examiner has failed to offer any arguments or cite any references to establish "that one of ordinary skill in the art would reasonably doubt" that polypeptides differentially expressed in certain tumors can be used as a diagnostic tool. Haynes *et al.*, Gygi *et al.*, Chen *et al.*, Fessler *et al.*, and Hu *et al.* do not support the Examiner's position and are not contrary to Applicants' asserted utility. Likewise, the Examiner has not offered any substantial arguments or evidence to rebut the numerous declarations and references Applicants' have submitted in support of their

asserted utility. Given the lack of support for the Examiner's position, Applicants submit that the Examiner has not met her initial burden of overcoming the presumption that the asserted utility is sufficient to satisfy the utility requirement. And even if the Examiner has met that burden, the Applicants' supporting rebuttal evidence is sufficient to establish that one of skill in the art would be more likely than not to believe that the claimed antibodies can be used as diagnostic tools for cancer, particularly lung cancer.

Specific Utility

The asserted substantial utilities are specific to the claimed antibodies

Applicants next address the Examiner's assertion that the asserted utilities are not specific to the claimed antibodies related to PRO300. Applicants respectfully disagree.

Specific Utility is defined as utility which is "specific to the subject matter claimed," in contrast to "a general utility that would be applicable to the broad class of the invention." M.P.E.P. § 2107.01 I. Applicants submit that the evidence of differential expression of the PRO300 gene in certain types of cancer cells, along with the declarations and references discussed above, provide a specific utility for the claimed antibodies.

As discussed above, there are significant data which show that the gene encoding the PRO300 polypeptide is expressed at least two-fold higher in lung tumor tissue compared to normal lung tissue. These data are strong evidence that the PRO300 gene and polypeptide are associated with lung tumors. Thus, contrary to the assertions of the Examiner, Applicants submit that they have provided evidence associating the PRO300 gene and polypeptide with a specific disease. The asserted utility as a diagnostic tool for cancer, particularly lung tumor, is a specific utility – it is not a general utility that would apply to the broad class of antibodies.

Conclusion

The PTO has asserted two arguments to support its conclusion that based on the cited literature, one of skill in the art would not assume that higher expression of mRNA would correlate with increased polypeptide levels: (1) the Examiner asserts that Applicants' disclosure and evidence lacks critical necessary details, such as significance of expression levels, the probability that the claimed antibodies will detect tumor tissue, and an identification of the particular type of lung tumor for which PRO300 polypeptides are useful as diagnostics; and (2)

the Examiner cites Haynes *et al.*, Gygi *et al.*, Chen *et al.*, Fessler *et al.* and Hu *et al.* to support her assertion that mRNA levels are not predictive of protein levels. The Examiner states that further research needs to be done to determine if the increase or decrease in PRO300 DNA supports a role for the peptide in cancerous tissue. Applicants have addressed each of these arguments in turn.

First, the Applicants provided a first Declaration of Chris Grimaldi stating that the gene expression data in Example 18 are real and significant. This declaration also indicates that given the relative difference of at least two-fold in expression levels, the disclosed nucleic acids and corresponding polypeptides and antibodies have utility as cancer diagnostic tools. The PTO has not offered any substantial reason or evidence to question the data in Example 18, or the first Grimaldi Declaration.

Second, Applicants have shown that the second Grimaldi Declaration and Polakis Declaration, the accompanying references, as well as the excerpts and references cited above, demonstrate that it is well-established in the art that a change in mRNA levels generally correlates to a corresponding change in protein levels. Haynes *et al.*, Gygi *et al.* and Hu *et al.* do not address this issue, and are not contrary to Applicants' asserted utility. Portions of Chen support Applicants' position, while the remainder is not contrary to Applicants' assertion that generally there is a correlation. Likewise, Fessler is not contrary to the assertion that a change in the level of mRNA for a particular protein generally leads to a corresponding change in the level of the encoded protein. As shown by the declarations, references, and textbooks discussed below, Applicants submit that the understanding in the art is that generally there is a correlation between a change in mRNA level and a change in protein level. In fact, the working hypothesis among those skilled in the art, as illustrated by the evidence presented by Applicants, is that there is a positive correlation between changes in mRNA levels and changes in protein levels for a particular gene.

Thus, the Examiner has not offered any substantial reason or evidence to question Applicants' declarations and supporting references.

Third, Applicants have shown that it is not necessary to know what role PRO300 plays in cancer to use it and its associated antibodies as diagnostic tools. The Examiner's own guidelines recognize this fact, and numerous patents have issued which claim differentially expressed

polypeptides and antibodies to the same, or methods employing such polypeptides and antibodies.

Given the totality of the evidence provided, Applicants submit that they have established a substantial, specific, and credible utility for the claimed antibodies as diagnostic tools. According to the PTO Utility Examination Guidelines (2001), irrefutable proof of a claimed utility is not required. Rather, a specific, substantial, and credible utility requires only a "reasonable" confirmation of a real world context of use. Applicants remind the PTO that:

> A small degree of utility is sufficient . . . The claimed invention must only be capable of performing **some** beneficial function . . . An invention does not lack utility merely because the particular embodiment disclosed in the patent lacks perfection or performs crudely... A commercially successful product is not required... Nor is it essential that the invention accomplish all its intended functions... or operate under all conditions... partial success being sufficient to demonstrate patentable utility... In short, **the defense of non-utility cannot be sustained without proof of total incapacity**. If an invention is only partially successful in achieving a useful result, a rejection of the claimed invention as a whole based on a lack of utility is not appropriate. M.P.E.P. at 2107.01 (underline emphasis in original, bold emphasis added, citations omitted).

Applicants submit that they have established that it is more likely than not that one of skill in the art would reasonably accept the utility for the claimed antibodies relating to PRO300 set forth in the specification. In view of the above, Applicants respectfully request that the Examiner reconsider and withdraw the utility rejection under 35 U.S.C. §101.

Rejection under 35 U.S.C. §112, first paragraph – Enablement

The Examiner has maintained the rejection of Claims 1-5 under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to use the invention. The Examiner argues that because the claimed invention is not supported by a substantial, specific and credible utility, the claims are not enabled.

Applicants submit that in the discussion of the 35 U.S.C. § 101 rejection above, Applicants have established a substantial, specific, and credible utility for the claimed antibodies. Applicants therefore request that the Examiner reconsider and withdraw the enablement rejection to the extent that it is based on a lack of utility for the claimed antibodies.

Rejection Under 35 U.S.C. § 112, Second Paragraph - Definiteness

The Examiner has rejected Claims 1-5 as allegedly being indefinite for failing to particularly point out and distinctly claim the invention. In particular, the Examiner argues that the term "specifically" recited in Applicants' claims renders the metes and bounds of the claims unclear. The Examiner states that "it is not clear if there is a basis in the instant specification as filed," for the term "specifically." Office Action at 21. According to the Examiner, "an antibody will bind the amino acids of the antigenic portion in whatever protein the sequence is located." *Id.*

Applicants submit that paragraph [0246] clearly defines "an antibody that 'specifically binds to' or is 'specific for' a particular polypeptide or an epitope on a particular polypeptide" as "an antibody that binds to that particular polypeptide or epitope on a particular polypeptide without substantially binding to any other polypeptide or polypeptide epitope." Applicants submit that given the precise meaning of "specifically" in relation to antibody binding provided in the specification, the metes and bounds of Applicants' claimed invention are clear to those skilled in the art.

The Examiner also states that "a new ground of rejection for lack of enablement and/or written description may be required," should Applicants intend the term to mean that the antibody binds the recited protein and no other protein. As discussed below, such rejections would be improper.

An application enables the claims "if one skilled in the art, after reading the[] disclosure[], could practice the invention claimed ... without undue experimentation." *Chiron Corp. v. Genentech, Inc.*, 363 F.3d 1247, 1253 (Fed. Cir. 2004). While the application must enable one of ordinary skill in the art to practice the full scope of the claimed invention, "[t]hat is not to say that the specification itself must necessarily describe how to make and use every possible variant of the claimed invention, for the artisan's knowledge of the prior art and routine experimentation can often fill gaps, interpolate between embodiments, and perhaps even extrapolate beyond the disclosed embodiments, depending upon the predictability of the art." *AK Steel Corp. v. Sollac*, 344 F.3d 1234, 1244 (Fed. Cir. 2003) (Emphasis added).

Here, Applicants disclose the amino acid sequence of SEQ ID NO:12 and claim antibodies that specifically bind to SEQ ID NO:12. The law has established that it is well within those of skill in the art to make antibodies which are specific to a disclosed sequence. In the seminal case regarding the enablement standard, the Federal Circuit reversed the Board's decision of non-enablement and held that as of 1980, undue experimentation was not required to make antibodies specific to a target peptide. *In re Wands*, 858 F.2d 731 (Fed. Cir. 1988). Nevertheless, in paragraphs [0366]-[0407], Applicants provide detailed methods regarding how to make and use antibodies that specifically bind PRO polypeptides. Accordingly, the skilled artisan would certainly be able to make the claimed antibodies without undue experimentation.

Likewise, Applicants maintain that any possible Written Description rejection would also be improper. The well-established test for sufficiency of support under the written description requirement of 35 U.S.C. §112, first paragraph is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'" *Vas-Cath, Inc. v. Mahurkar*, 935 F.2d at 1562-63, 19 U.S.P.Q.2d at 1116 (citations omitted). The M.P.E.P. provides that "an applicant may. . .show that an invention is complete by disclosure of sufficiently detailed, relevant identifying characteristics. . .[such as] physical and/or chemical properties, functional characteristics when coupled with a known or disclosed correlation between function and structure, or some combination of such characteristics." M.P.E.P. 2163 (II) 3(a) (citations omitted). One factor to be considered in determining whether there is sufficient evidence of possession of an invention is the level of skill and knowledge in the art.

The present invention pertains to the field of recombinant DNA/protein/antibody technology. It is well-established that the level of skill in this field is very high since a representative person of skill is generally a Ph.D. scientist with several years of experience. Accordingly, the teaching imparted in the specification must be evaluated through the eyes of a highly skilled artisan as of the date the application was filed. Here, Applicants have described antibodies that specifically bind to polypeptides of SEQ ID NO:12, and that do not substantially bind to other polypeptides. Like a particular catalytic activity, the function of being able to specifically bind to SEQ ID NO:12 is directly related to the amino acid sequence of SEQ ID NO:12. Thus, the genus of antibodies that specifically bind to SEQ ID NO:12 possess a

described functional activity are adequately described. As such, Applicants were in possession of the common attributes or features of the claimed subject matter.

Rejection Under 35 U.S.C. § 102(b) – Anticipation

The Examiner has maintained the rejection of Claims 4-8 and 11-19 as being anticipated by WO 01/16318 to Eaton et al., to which Applicants claim priority. According to the Examiner, the claimed invention does not fulfill the requirements of 35 U.S.C. § 112, and thus Applicants are not entitled to the benefit of WO 01/16318, and cites the same against Applicants' present application.

Under 35 U.S.C. § 120, an applicant is entitled to the benefit of the filing date of an earlier filed application that discloses the same invention in the manner provided by 35 U.S.C. § 112, first paragraph, provided the applicant properly claims priority to the earlier application. In a preliminary amendment filed on September 3, 2002, Applicants made specific reference to WO 01/16318, claiming priority thereto. WO 01/16318 contains the same disclosure relating to PRO300 and its utilities as the instant application, including the data in Example 18. For the same reasons detailed above in the Remarks addressed to the rejections under 35 U.S.C. § 101 and 112, Applicants submit that WO 01/16318 is enabling for and adequately describes the claimed invention. Therefore, because Applicants have properly claimed priority to WO 01/16318, and because WO 01/16318 satisfies the requirements of 35 U.S.C. § 112, Applicants are fully entitled to the benefit of the filing date of WO 01/16318 and it cannot be prior art to the present application. Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. § 102(b).

CONCLUSION

In view of the above amendments and remarks, Applicants respectfully maintain that the claims are patentable and request that they be passed to issue. Applicants invite the Examiner to call the undersigned if any remaining issues may be resolved by telephone.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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Dated: Nov. 30, 2005

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